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Implications of Heavy Metals on Human Cancers

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Abstract

Heavy metals have far-reaching impacts on human health and implications for the development and proliferation of human cancers. Cautions have been increasing over the presence of heavy metals in the environment and their effects on health, particularly the possibility that they could cause cancer in people. Investigation on the tumorigenesis capacity of heavy metals is ongoing since such compounds' impact on human health remains a serious health issue. Human exposition to aluminum, arsenic, beryllium, cadmium, lead, mercury, and nickel as well as the possibility of cancer from these elements have been of significant interest. This review paper explores the multifaceted impact of heavy metals on human cancer development, overall exposure rates to various causing metals, and different strategies to mitigate such human cancers by adapting technical and environmental techniques. We delve into the mechanisms by which heavy metals can induce cellular transformation, including oxidative stress, DNA damage, and disruption of cellular signalling pathways. Additionally, we examine the role of heavy metals in modulating the immune response, contributing to cancer progression.

Subject Areas

Environmental Sciences

Keywords

Heavy Metals, Cancer, Development, Human Health

1. Introduction

Heavy metals have been historically linked to serious medical problems affecting the well-being of the masses worldwide. The metals that cause these harmful alterations in human well-being must be considered, with particular attention paid to their cancerous potential. Metal toxicity effects on human health have been widely known and researched [1]. The primary, source of injury from non-essential metallic substances like cadmium, mercury, nickel, and lead is that they disrupt metabolism by replacing necessary divalent cations (like calcium, magnesium, iron, as well as zinc), in proteins, enzymes, and hard tissues like bones and teeth. Whenever the level of trace elements surpasses specific physiological thresholds, they may be harmful to humans [2]. This is especially true of their redox activity, which, except zinc, can cause oxidative stress, the synthesis of reactive oxygen species, and other reactions in Fenton (Fe) or Fenton-like (Cu, Cr, etc.) reaction chains. The various characteristics of heavy metals including their solubility, oxidation states, hardness or softness, binding attitudes, and the existence of several forms that might affect their diversity in biological systems are associated with the cellular harm these elements cause [3] (see **Table 1**).

Cancer and tumour formation have been related to prolonged exposure to certain heavy metals and their constituents. For instance, it is hypothesised that cadmium mimics oestrogenic actions because of its capacity to attach to the oestrogen receptor's hormone-binding region with high affinity, which accelerates the growth of breast cancer [4]. It has been additionally discovered that the buildup of cadmium raises the incidence of lung cancer and that people with lung cancer who have high levels from exposure to such heavy metal would have an unfavourable outcome. Furthermore, it is hypothesised that several heavy metals, such as chromium, nickel, and cadmium, will disrupt the lining of the gastric barrier, causing swelling and tissue damage as well as gastric malignancies [5]. As cadmium, chromium, and nickel have been categorised as group one carcinogens by the International Agency for Research on Cancer. These substances increase the likelihood of developing cancer and diseases linked to cancer, including high blood pressure, diabetes, rheumatoid arthritis, heart failure, lung disease, and kidney problems. They also cause damage to DNA, oxidative stress, and cellular death mechanisms. When taken as a whole, these metals pose an important ecological danger for the emergence of various kinds of cancer. Research on a variety of species, including humans and aquatic mosses, has demonstrated that heavy metals may harm biomarkers found in the bloodstream, tissues, skin, and nails that are connected to the generation of reactive oxygen species (ROS) [6] (see **Table 2**).

Table 1. Exposure cases to these metals and potential risk factors.

Metal	Global exposure cases per year	Exposure level thresholds	Cancer cases related to exposure	Industries with the highest risk of exposure	References
Aluminum	Not well-documented globally, but significant in industrial settings	Occupational exposure limit (OEL) varies by country, typically around 5 mg/m^3 (OSHA)	Limited direct evidence linking aluminum to cancer, but some studies suggest a possible link to breast cancer and neurodegenerative diseases	Aluminum production, automotive, construction, and packaging industries	[7]
Arsenic	Estimated 200 million people exposed globally	World Health Organization (WHO) guideline for drinking water: 10 µg/L	Arsenic exposure is linked to lung, skin, and bladder cancers. Estimated 200,000 - 300,000 new cancer cases annually	Mining, smelting, and wood treatment industries	[8]
Cadmium	Significant exposure in industrial and agricultural settings	OEL: 5 µg/m^3 (OSHA)	Cadmium exposure is linked to lung and prostate cancers. Estimated 10,000 - 20,000 new cancer cases annually	Battery manufacturing, electroplating, and pigments industries	[9]
Lead	Estimated 120 million people exposed globally	OEL: 0.05 mg/m^3 (OSHA)	Lead exposure is linked to brain and kidney cancers. Estimated 50,000 - 100,000 new cancer cases annually	Battery manufacturing, smelting, and painting industries	[10]
Mercury	Significant exposure in mining and industrial settings such as 200,000 - 300,000 tons emitted annually	OEL: 0.05 mg/m^3 (OSHA)	Mercury exposure is linked to kidney and brain cancers. Estimated 10,000 - 20,000 new cancer cases annually	Mining, chlor-alkali, and dental industries	[11] [12]
Nickel	Significant exposure in industrial settings	OEL: 1.0 mg/m^3 (OSHA)	Nickel exposure is linked to lung and nasal cancers. Estimated 20,000 - 30,000 new cancer cases annually	Nickel refining, welding, and battery manufacturing industries	[9]
Chromium	Significant exposure in industrial settings	Air: 0.01 mg/m^3 (OSHA) for Cr(VI)	5000 - 15,000 annual cancer cases (lung, nasal)	Chrome plating, leather tanning, pigment production	[13]

Table 2. Illustrates the roles and mechanism of actions of heavy metals in cancer development and progression of human cancer.

Metal	Functions	Mechanisms of action	Roles in cancer	References
Aluminum	Component of clay minerals, used in various industrial products	Induces oxidative stress, disrupts calcium homeostasis, and interferes with neurotransmitter function	Co-carcinogen and potentiates other carcinogens	[14]
Arsenic	Found in soil and water, used in pesticides and herbicides	Interferes with DNA repair, induces oxidative stress, and activates oncogenes	Carcinogens disrupt the cell cycle	[15]
Beryllium	Used in alloys and ceramics	Induces oxidative stress, damages DNA, and interferes with cell signaling	Carcinogenic potentials	[16]
Cadmium	Found in soil and water, used in batteries and pigments	Induces oxidative stress, damages DNA, and interferes with zinc metabolism	Carcinogenic in nature	[17]
Lead	Used in batteries, paints, and plumbing	Interferes with heme synthesis, disrupts neurodevelopment, and damages kidneys	Neurotoxin and potential carcinogen	[18]
Mercury	Found in fish and seafood, used in dental fillings and thermometers	Induces oxidative stress, damages DNA, and interferes with neurotransmitter function	Neurotoxin and potential carcinogen	[19]
Nickel	Found in soil and water, used in stainless steel and batteries	Induces oxidative stress, damages DNA, and interferes with cell signaling	Carcinogenic in nature	[20]

1.1. Aluminum

Because of its many approaches of action and listing as a carcinogen, aluminium is unlike other metals. Humans are typically exposed to aluminium through contaminated foods, curiously throughout the production of human immunisations, while aluminium is incorporated as a chemical salt throughout several industrial operations that produce goods for sale. There is an immediate correlation between human cancer, specifically breast cancer, and aluminium exposure [21]. Moreover, the same variety of aluminium employed to synthesis human deodorant and antiperspirant deodorants is similarly used in mice. These investigations showed that exposure to AlCl3 caused malignant alterations in mammary gland epithelial cells. After being exposed to human breast tissue epithelial cells, comparable outcomes were reported. Aluminium has been connected to neoplasia expansion, particularly sarcoma formation [22].

The expression levels of the tumour suppressor gene BRCA1 mRNA were shown to be lower in vitro investigations involving human breast cells subjected to aluminium. This result coincided with additional preservation genes that control normal DNA levels declining in expression. In a related investigation, scientists exposed human cancerous breast cells to aluminium and recorded the constant induction of unchecked cell proliferation [23]. The aluminium behaved as a metalloestrogen, which means the reaction worked as a competitor for the oestrogen receptor complex on these breast cells, according to the investigators' review

of these data. The capacity to cause cancer after exposure to aluminium has been linked to this type of metabolic process. Research on the physiology of humans has shown that aluminium builds up in the skeletal and soft tissues after oral administration. Aluminium chelate is intended to strike those tissues. When detoxifying aluminium exposure, desferrioxamine is among the most often utilised chelating agents. Although desferrioxamine has a level of toxicity that corresponds to its clinical application in humans, this chelator has shown to be particularly successful in eliminating the heavy metal aluminium from tissue [24]. There is still an additional method to cut down on aluminium, particularly if it is shown to be found in large quantities in everyday products (drinking water, for example). Reverse osmosis filtration is the technique applied in these circumstances. Application of the process in various industries, including copper mining along with various industrial purposes, has shown substantial decreases in aluminium levels. Aluminium functions similarly to physiological oestrogens by adhering to cellular oestrogen receptors, a property of metalloestrogens, an inorganic xenoestrogen class. Aluminium chloride and aluminium chlorohydrate are among the most often utilised aluminum-based chemicals in underarm cosmetic products (UCP). Aluminium ions not only cause DNA DSB, but they also cause oxidative stress, cell division, and disruption of oestrogen action both before and during metastasis [25].

According to another investigation, human skin absorbs aluminium hydroxide produced by the reaction of aluminium chloride and aluminium chlorohydrate in an aqueous solution with a pH of 7.0. This implies that an ongoing route of aluminium exposures for the human mammary epithelium is indicated by the everyday application of UCPs to the area beneath the arms [26]. After aluminium has a transformative impact, DNA DSB appears in a dose-dependent manner. Removing the salt has not yet changed the phenotypic of MCF-10A cells that developed in the presence of aluminium chloride. These findings indicate that aluminium-altering activity is caused by a mutagenic effect, at least in parts. Genes controlling cellular motility, death, metastasis, and proliferation are mutated by the salt. The specific genes that control the T-lymphoma incursion and metastasis-inducing protein 2 (Tiam2), the Max-binding protein MNT, and the other proteins are also going to be mutated. As a pro-survival protein, MNT inhibits the pro-apoptotic action of the MYC protein family, which is involved in oncogenesis. Human cancers and neurone growth are significantly impacted by the Tiam2 gene [27].

1.2. Arsenic

Arsenic is a heavy metal which, when in contact with human tissues, is known to be cytotoxic and can cause major ailments in individuals who are exposed. Usually, eating foodstuffs and drinking water reservoirs stained with arsenic is the route of contact. There are instances of occupational exposure to arsenic caused by pollution in the atmosphere as well. Considering arsenic has been found in tumour tissue, the relationship between exposure to heavy metal arsenic and ma-

lignancies in humans is significant [15]. Research which precisely shows an association between arsenic and the progression of bladder, lung, and skin cancers provided a specific demonstration of the connection between arsenic and cancer progression. The association between arsenic exposure and fatalities among individuals with a range of cancers, including colon, stomach, kidney, lung, and nasopharyngeal cancers, was the subject of further positive connection associating arsenic with the emergence of human cancers. Crucially, epidemiological evidence from multiple research demonstrates a strong correlation between persistent low-level arsenic exposure and the onset of non-Hodgkin's lymphoma and pancreatic cancer [28] [29].

Regarding arsenic, numerous investigations have unequivocally shown that the processes behind arsenic-induced carcinogenicity entail the generation of reactive oxygen species (ROS), which produces crucial epigenetic modifications that result in detrimental DNA repair pathways. In particular, these significant epigenetic modifications brought about by arsenic exposure have involved modifications to DNA methylation, histones, and miRNA, all of which may be accountable for the carcinogenic effects of exposure to arsenic. The potential of arsenic to cause aberrant cell development cycles in particular cell types, like macrophages and lung epithelial cells, is an additional hypothesis on the pathway of action for arsenic-associated carcinogenicity [30]. There has been another theory put up to clarify why arsenic is carcinogenic. One another method was discovered after human bladder cells were exposed to arsenic. The process was linked to arsenic's capacity to suppress normal cellular morphology due to the changed expression of genes that are in charge of base excision repair after long-term exposure. The rate-limiting phase, which is catalysed by the active enzyme DNA polymerase beta, is the main enzymatic constituent in this process. Higher levels of arsenic corresponded to a decrease in the activity of enzymes, as seen by the dose-dependent reduction of enzymatic activity in the existence of arsenic. According to these investigations, long-term exposure to arsenic changed the function of some genes that regulate cellular growth as well as the shape of cells [31].

To optimise anti-cancer and minimise oxidative stress, it is advised to include antioxidants in eating habits when discussing the therapy and elimination of arsenic. Since both rice and apple juice include high concentrations of vitamin C, a powerful antioxidant, it has been discovered that their antioxidant contents lessen cellular stress. One of the main causes of many cellular diseases is oxidative stress [32]. The smallest permitted amount of toxicity exposure for arsenic is 5 μg/L. Following the discovery of these dietary connections, further strategies for reducing food-related toxicity have been put up. One such strategy involves genetically modifying rice to prevent arsenic from being absorbed. Utilising specific microbial species that lessen metal absorption when they interact with arsenic in the atmosphere served as another tactic [33].

Research has indicated that As^{3+} plays a role as an environmental etiological component in a subset of human malignancies. Research has demonstrated a

noteworthy association between As^{3+} exposure in the surroundings, whether from pollutants in the air or contaminated drinking water, and lung cancer in humans. As^{3+} gets absorbed by the bloodstream when it is consumed from drinking water. Because of the high relative pressure of oxygen, its products of metabolism, particularly the methylated As^{3+}, may accumulate in the lung tissues [34]. Although the precise pathophysiological mechanism by which arsenic causes cancer is yet unknown, aberrant immunological development, chromosome abnormalities (with uncontrollable growth), and an increase in oxidative stress are possible possibilities. One significant type of oxidative damage to DNA that was picked up from the urine and skin tissues of people exposed to arsenic is called reactive oxygen species. Among the initial genetic impacts found in people exposed to arsenic were breakage in DNA strands, micronuclei in cord blood, and nitrative DNA damage. According to studies, arsenic also interferes with the system that repairs DNA. As a result, oxidative DNA damage and mutations are caused by the inhibition of DNA ligase, nucleotide excision repair, DNA base excision repair, and DNA strand break rejoining [35].

Furthermore, arsenic modifies epigenetic controls. The DNA of the arsenic-exposed person has hypermethylation of the critical promoter regions of the p53 and p16 genes. Given that elevated arsenic exposure is linked to p53 and p16 gene DNA hypermethylation, it is possible that arsenic causes cancer by epigenetic silencing of those crucial tumour suppressing genes. According to the latest findings, arsenic can change the sequences of miRNA expression in both in vitro and in vivo models of arsenic-induced carcinogenesis [36]. Disrupted miRNAs may function as an entirely novel group of oncogenes or tumour suppressive genes, contributing to the initiation and spread of cancer. MicroRNAs play an important role in the development of tumours. For instance, overexpression of miR-504 inhibits the p53 gene, reducing p53-mediated apoptosis and also adversely affecting the cell cycle arrest that occurs during stressful situations. One of the most extensively studied ways to combat arsenic carcinogenicity is the formation of reactive oxygen species (ROS), which interacts with DNA to cause structural destruction of DNA, which leads to genetic abnormalities. Additionally, overexpression of antioxidant enzymes can desensitise cells to apoptosis [37].

1.3. Beryllium

The heavy metal beryllium is connected to humans' consumption due to its severe use. Therefore, it has been shown that environmental pollution caused by human consumption most frequently results from its interaction with power plants, where it is frequently detected in debris. Thus, the absolute most prevalent manner in which humans come into contact with one another is by breathing [22]. It is a known environmental pollutant that has been connected to lung cancer and other respiratory illnesses. Although there was initial doubt about the link between beryllium and lung cancer, more research showed that exposure to the metal was associated with the disease, particularly after extended periods of ex-

posure. It was later demonstrated that the dentistry industry's usage of beryllium presented an additional danger of exposure at work [38]. As a result, the use of personal protective equipment (PPE) significantly reduced occupational exposure to dental-related hazards. Crucially, it was discovered that patients with stage III breast cancer had higher than normal beryllium content. However, there were other heavy metals found in this investigation than beryllium, which limited the possibility of an immediate cause-and-effect scenario [39].

The relationship between increased lung-resident CD4+ T-cell numbers and the cytokine tumour necrosis factor-alpha (TNF-α) represented one of the numerous carcinogenic mechanisms investigated. This component is crucial to the initiation and progression of inflammatory conditions. The correlation found between TNF-α and beryllium suggests a clear connection to the effects of long-term involvement in inflammation [40]. The p16 gene, a recognised tumour suppressive gene that is triggered after exposure to beryllium, was demonstrated to methylate due to genetic alterations linked to beryllium exposure. The majority of beryllium's carcinogenic qualities have been shown in the metal form, as well as in certain types of its various alloys and various kinds of components. The primary cause of beryllium-induced lung cancer is pulmonary instillation or inhalation, which has an immediate effect on the lung. Because of beryllium's inclination towards bone, it can cause bone tumours, which is a feature of osteogenic sarcoma [41].

1.4. Cadmium

As a hazardous substance found in the atmosphere, cadmium is a heavy metal that can have serious negative effects on well-being. The industries where this substance exists in its emissions are typically linked to the origins of ecological exposure. The component was found to be used in mining, metallurgical research, battery development, and prevention of pigment precipitation in textiles and apparel. Soil contamination is a highly important problem when it comes to environmental cadmium exposure because the majority of human exposure to cadmium occurs through ingestion of contaminated food or drinking water, inhalation, and/or smoking. In terms of soil pollution, dumps are one particular source of cadmium contamination [18]. Cadmium concentrations in dumps are far greater than what is considered manageable for maintaining human well-being. Human exposure to cadmium is typically linked to the consumption of contaminated foods, as landfills are a significant source of contaminants in water and soil. Cadmium's primary health concern is that it can cause cancer in people who are exposed to high levels of the metal [42]. This includes malignancies of the breast, oesophagus, intestines, lungs, stomach, testes, and even the gallbladder. Studies that have looked at the relationship between gallstones and pre-cancerous conditions in individuals who have gallbladder cancer have found that these conditions are often linked to heavy metal exposure. Cadmium and other heavy metals have been reported to be higher when analytically substantial amounts of heavy metal

content were examined. There is still serious worry for human health regarding the connection between cadmium and carcinogenicity [43].

The oncogenic alteration of liver cells cultivated in the emergence of cadmium was shown in different types of studies, specifically laboratory-generated tests. Significant amounts of cadmium were found among individuals with gliomas, or brain cancer, according to heavy metal assessment. This proposes that exposure to heavy metals may be associated with a cancerous brain. The pancreas is an additional organ in the human body that has been connected to cancer after cadmium exposure [44]. The emergence of blood diseases, specifically chronic myeloid and lymphoblastic leukaemia, has been further connected to cadmium. Individuals with leukaemia were shown to have greater levels of cadmium in their bloodstreams and urine when contrasted with controls, despite having a lower concentration of magnesium. The link between cadmium in urine and the occurrence of intestinal cancer is another important linkage between elevated cadmium levels and carcinogenicity. Similar to what was seen alongside other heavy metals, its general effects were linked to the emergence of various malignancies, which prompted research into the specific pathways that triggered the carcinogenic actions [45]. The production of reactive oxygen species (ROS) and epigenetic modifications were the main components of the carcinogenic process associated with cadmium. Both played a part in limiting the ability of repair systems to produce broken or changed DNA [46].

Both also had a role in the afflicted cells' failure of apoptosis. Whenever cadmium exposure is prolonged or acute, the outcome affects the modified pathways of signalling that lead to changed gene expression, all of which are involved in the start of tumour formation. The essential proteins have been altered in this crucial series of intracellular alterations that occur after cadmium exposure, either by up-regulation or increased activity or even by inhibition of essential molecular pathways [47]. One such instance is the inhibition of EGR-1, a crucial protein that controls processes that are detrimental to cells, such as transcription. Polypeptide ligands with cadmium selectivity are among the substances created to lessen cadmium toxicity. The primary explanation for this is that flavonoid chemicals are extensively available, which means they exist organically [48]. Generally speaking, flavonoids are present in all vegetables and fruits. Because flavonoids are strong antioxidants, they may help chelate cadmium and effectively inhibit the production of reactive oxygen species (ROS). Nevertheless, there is still much to learn about flavonoids, and in particular, how their arrangement inhibits the progression of cadmium toxicity [49].

Research evidence exists to investigate the potential efficacy of stem cell therapy in mitigating the harm to cells resulting from cadmium poisoning. Cadmium exposure caused damage to tissues in the testicles of rats used in an investigation. Mesenchymal stem cells obtained from bone marrow were given to the mice after they were exposed to toxins. After receiving medical attention, it was found that the testes' levels of the apoptosis-causing proteins had returned to normal, affect-

ting the function of cells. There was proof that the injured tissue had successfully healed within the impacted tissue. These findings showed that the repair of mitochondrial apoptosis was the aim of healing provided by mesenchymal stem cells [50]. The capacity of the immune system to respond to cadmium exposure is restricted, and the metal cannot be metabolically broken down into less hazardous forms, making cadmium a deadly metal for humans. One hazardous metallic element that is frequently referred to as an individual carcinogen is cadmium. Food, tobacco smoke, and industries connected to the cadmium industry are the primary causes of their exposure [51]. It is estimated that the most significant process in cadmium-induced carcinogenesis is reactive oxygen species (ROS). Reactive oxygen compounds can cause intracellular oxidative stress, which may destroy macromolecules and ultimately play a role in the development of cancer. Although cadmium can not bind to DNA directly, it can cause oxidative stress, which may cause DNA impairment unintentionally. Participating in chemical processes of the Fenton type does not start the procedure. A redox pair consisting of a ferrous ion and hydrogen peroxide (H2O2) is what defines the Fenton reaction, which produces a reactive hydroxyl radical in the end. Cadmium-induced cancer may arise through many pathways such as abnormal gene expression and signal transduction, repressed apoptosis, interfered with E-cadherin-mediated cell-cell adhesion, and modified repaired DNA [52].

1.5. Lead

Lead has long been known to pose a serious threat to the environment. Numerous mechanisms have been implicated in compromising human health, either independently or in combination, particularly with prolonged exposure to lead. Environmental pollution of soil and water, particularly from drinking water sources, is a fairly prevalent way that humans are exposed to lead. Lead eventually ends up in food that is ingested because lead levels build up in deposits and exposure manifests through the human food chain. The lead additive that was added to gasoline was another frequent source of lead that increased human exposure to the metal [53]. The finding that lead was found in cigarette smoke was a concerning connection to human lead exposure; as a result, smokers' blood lead levels were reported to be high because there is no acceptable amount of lead in terms of its effects on human health. There are additional workplace dangers, such as mining, which puts workers at risk for lead exposure. Research is currently ongoing to determine if exposure to lead causes a particular type of cancer directly or indirectly. Specifically, rather than being an initiating agent, interest has focused on a supportive, maybe additive, function in the maintenance of cancer [54]. Lead has been found in conjunction with other heavy metals that are also well-known to have negative effects on human health, particularly in young children where lead can interfere with myelin formation and impede the progression of the central and peripheral nervous system. For instance, when gliomas (brain cancer) patients were examined, extremely high levels of lead and cadmium were found in

Flint, Michigan's water systems. This observation showed that the presence of many heavy metal pollutants in human tissue or bodily fluids can have a more detrimental effect on human health [55]. According to a study of kidney cancer patients, excessive lead levels were linked to the development of the malignancy. Evidence was found that reinforced this observation, tying blood lead levels to the development of cancer of renal cells. There may be a connection between lead levels and gallbladder disease, possibly resulting in the formation of a precancerous lesion, as evidenced by the development of liver disease linked to elevated lead concentration levels and several other heavy metals when measured in gallstones [56].

Examining workers who had been exposed to high levels of lead showed that there was a strong positive correlation between heavy metal and lung cancer, as well as a positive interdependence between lead exposure and the progression of cancer within the tissues of the brain, larynx, and bladder. Increased levels of lead and several other heavy metals were measured in patients who had been diagnosed with pancreatic cancer, indicating that exposure to heavy metals may increase the overall carcinogenicity of these metals [57]. Lead efficiently interferes with internal genetic processes, causing damage to DNA and blocking its repair, which makes tumor regulatory genes incapable of controlling tumor growth. Studies on animals utilizing mice exposed to lead demonstrated that the heavy metal may produce reactive oxygen species (ROS) and that this effectively changed the sequence of certain genes that function. The findings demonstrating lead was efficient in normal reactions governing transcription was another crucial insight into lead's capacity to interfere with regular physiological processes within cells. The change from zinc to lead, which acts as a metal catalyst for several important enzymatic activities that regulate DNA transcription, was the reaction that mediated this transformation [58].

This observation was accompanied by the significant correlation that calcium played in these enzymatic activities, as demonstrated by epidemiological research that linked higher levels of calcium to a lower incidence of renal cell carcinoma. As a result, as the researchers noted, it was evident that a clinical study was required to ascertain the overall relevance of the interaction between these crucial cations and heavy metals. One metal that can be categorized as a contaminant to the environment is lead, which is well-known for being used in several industrial settings across the globe. Health impacts from high lead exposure might include neurological and brain damage, gastrointestinal issues, anemia, liver and kidney damage, problems with fertility, and developmental delays [59]. Another substance that is suspected of being carcinogenic is inorganic lead; epidemiological data demonstrates that industrial workers exposed to inorganic lead have a considerably increased risk of stomach, lung, kidney, brain, and meningeal malignancies. Oxidative damage, apoptosis induction, modified cell-signalling pathways, suppression of DNA synthesis and damage repair, and interaction with DNA-binding proteins are the mechanisms that contribute to their involvement in

carcinogenesis [29]. According to the results of one research, there is a connection between cancer of brain risk and occupational lead exposure. Brain cancer death rates among industrial workers who might have been exposed to lead were higher than those of participants who were not exposed, and there was evidence of an exposure-response relationship [60].

1.6. Mercury

Mercury is another heavy metal that has been demonstrated to have serious negative effects on human health after exposure. The majority of mercury exposure results from environmental exposure after industrial usage, with a small quantity of the heavy metal occurring in tiny levels as a mineral. Mercury consumption has hurt the ecosystem in a variety of ways. Common applications for mercury include its long-term use in dental fillings, thermometers, some battery types, and the incineration of medical waste. Mercury pollution has also been linked to the burning of fossil fuels [61]. The fact that mercury frequently vaporizes and enters the atmosphere together with other compounds that can later be absorbed into soils and water systems is another aspect that contributes to environmental pollution and mercury. There has been some evidence suggesting a connection between kidney cancer and mercury exposure and the development of cancer. This connection stems from the kidney's natural function of eliminating harmful compounds from the body when they are present, particularly in the blood. Both stomach and liver tumors are among the numerous cancers linked to mercury exposure. Mercury has been found in gallstones in notable amounts in people with gallbladder cancer, which is also connected to stomach and liver cancers. Mercury may have a role in the emergence of cancers that use certain systems to govern the growth of tumors. The ability to produce free radicals (ROS) and DNA disruption, whether linked to transcription processes or modifications or upkeep of its molecular structure, are the mechanisms involved [62].

Having said that, there are further documented carcinogenic pathways specific to mercury. One such mechanism that mitigates mercury's carcinogenic potential is its capacity to lower glutathione levels. Since glutathione is a naturally occurring antioxidant, as was previously mentioned, it can minimize the carcinogenic potential of mercury by reducing its antioxidant activity through reactive oxidant species [19]. This is achieved by inhibiting the development of oxidative stress mediated by reactive oxidant production. It has been shown that oxidative stress causes higher rates of lipid peroxidation in cells, which has been suggested as an additional functional mechanism causing cancer. Mercury has been linked to altering the activity of microtubules in cells, which can interfere with cellular mitosis by design. Given that mercury is so determined in the atmosphere, it is one of the most unstable heavy metals. Mercury causes apoptosis and oxidative damage [63]. A metalloestrogen, or tiny ionic metal that stimulates the estrogen receptor, is methylmercury (MeHg). Research suggests that the activation of the estrogen receptor by metalloestrogens leads to an upregulation of transcription and ex-

pression of genes regulated by estrogen, which in turn promotes the growth of estrogen-dependent breast cancer. The development of cancer occurs in four stages: promotion, latency, initiation, and progression. Mercury has been demonstrated to specifically inhibit the selenocysteine antioxidant enzymes during the promotion phase, resulting in an imbalance in the equilibrium of reactive oxygen species. Mercury satisfies the requirements to cause both the release of proinflammatory cytokines and a blockage of gap junction intercellular communication. These two methods could release cells from the homeostasis unique to their tissue, thereby encouraging their growth [64].

1.7. Nickel

Exposure to environmental contamination leads to the buildup of nickel within the tissues and organs of affected species. For instance, fish can introduce nickel into the food chain. Alternatively, once soil contamination occurs, there is yet another possible course of action. On an industrial level, nickel is frequently found in emissions from oil refineries that have been shown to be important sources of pollution and environmental exposure, raising the risk of exposure for local inhabitants who live close to these refineries. Human exposure to nickel has been linked to the emergence of numerous malignancies [65]. Evidence from epidemiological research has demonstrated a link between nickel exposure and the development of lung cancer as well as cancer in the tissues of the nose, sinuses, and throat. When blood serum was tested for nickel in breast cancer patients, the results showed a considerable elevation, indicating a possible link between high nickel levels and the development of breast cancer [4]. Acute myeloid and lymphoblastic leukemia development has also been connected to the relationship between nickel exposure and cancer. Nickel's major method of action involves inducing oxidative cellular damage, which is why it is implicated as a carcinogenic agent [66]. When nickel levels were investigated, sufferers with pancreatic cancer showed higher levels, suggesting a positive collaboration, even though other heavy metals were detected. Furthermore, a study concluded that prolonged exposure to nickel and concurrent exposure to other heavy metals may be associated with the development of liver cancer and T-cell lymphoma. All of these reports' implications point to nickel's potential for cancer [67]. It has been shown that nickel exposure affects the transcriptional and regulatory state of mRNAs as well as microRNAs. The capacity of nickel to affect immunity and the immune response is involved in these reactions, particularly when it comes to inflammation and the immune system, which has also been linked to a major role in carcinogenicity. Research on nickel and how it affects the inflammatory response has been done on both animal models and human cells. The findings of these investigations indicated a correlation between nickel exposure and cancer [68]. Nickel is regarded as a significant heavy metal carcinogen, mostly due to its ability to harm DNA. Studies both in vitro and in vivo have shown that nickel directly binds to DNA and stimulates reactive oxygen species (ROS), both of which break DNA pro-

cesses. In addition to directly inhibiting enzymes and down-regulating the expression of DNA repair molecules, nickel's carcinogenic characteristics also involve the suppression of DNA damage repair systems [69].

When reactive oxygen species damage DNA too much, it causes genomic instability, which is a factor in the development of tumors. Nickel overexposure is mostly caused by oxidative stress or genomic instability, which is a significant driving force behind oncogenesis. It is well-recognized that both endogenous and exogenous stressors can cause an excess of reactive oxygen and nitrogen species, which can lead to oxidative stress. Nickel's ability to bond with proteins, peptides, and amino acids facilitates the generation of these reactive oxygen species. The metal can dissolve in the human body and release ionic nickel, which is an active form of nickel that can infrequently cause genotoxic carcinogenesis [70]. In contrast to "non-genotoxic" carcinogens, which cause cancer by indirect or secondary mechanisms, "genotoxic" carcinogens are those that have the ability to directly change genetic material. Therefore, in terms of their carcinogenic processes, the majority of chemical carcinogens that cause direct damage to DNA are classified as "genotoxic". The ability of nickel to increase the intracellular concentration of nickel ions is another factor contributing to its carcinogenic potential. The nickel ions displace iron from the active site of dioxygenase enzymes and impede the membrane ion transporters, which exhaust intracellular iron. All of this results in their catalytic activity being inhibited. The carcinogenicity of nickel may be attributed to an epigenetic process involving DNA hypermethylation and the subsequent silencing of tumor suppressor genes [71].

2. Recent Advancements in Medical and Environmental Technologies to Reduce Exposure to Heavy Metals

The impact of heavy metals on human health, particularly in the context of cancer, has been well-documented. Recent advancements in medical and environmental technologies offer promising solutions to mitigate these risks. Chelation therapy involves the use of chelating agents to bind heavy metals and facilitate their excretion from the body. Common chelating agents include ethylenediaminetetraacetic acid (EDTA), dimercaptosuccinic acid (DMSA), and dimercaptopropane sulfonate (DMPS). These agents have shown efficacy in reducing the body's burden of heavy metals and improving health outcomes [72]. Advances in pharmacogenomics allow for the customization of treatment plans based on individual genetic profiles. This approach can optimize the effectiveness of chelation therapy and other interventions by tailoring dosages and treatment regimens to minimize side effects and maximize therapeutic benefits. Nanoparticles designed to target and sequester heavy metals show promise in reducing their bioavailability and toxicity. For example, magnetic nanoparticles can be used to remove heavy metals from contaminated environments and biological systems [73]. Phytoremediation is a cost-effective and eco-friendly method that uses plants to absorb, accumulate, and detoxify heavy metals from soil and water. Plants such as Thlaspi caerulescens

and Brassica juncea have been successfully used to remove metals like cadmium and lead from contaminated sites. Bioremediation involves the use of microorganisms to degrade or transform heavy metals into less toxic forms. Bacteria and fungi, such as Pseudomonas and Aspergillus, can metabolize heavy metals and reduce their environmental impact [74]. The development of advanced filtration systems, including reverse osmosis and nanofiltration, has significantly improved the removal of heavy metals from drinking water. These technologies can effectively reduce the concentration of metals like arsenic and lead, ensuring safer water supplies. Improved waste management practices, including the recycling of electronic waste (e-waste) and the proper disposal of industrial waste, can prevent the release of heavy metals into the environment. Recycling not only reduces pollution but also conserves resources [75].

3. Mitigation Strategies for Heavy Metals Across Different Regions and Industries

Heavy metals such as aluminum, arsenic, cadmium, lead, mercury, and nickel pose significant health risks, including the development of various cancers. Mitigation strategies to reduce the exposure and environmental impact of these metals vary widely across different regions and industries. On the one hand, developed countries generally have stricter regulations and more advanced technologies, while developing countries often face challenges in implementing and enforcing such measures. The Environmental Protection Agency (EPA) sets stringent standards for heavy metal emissions and discharges in the USA. The Safe Drinking Water Act (SDWA) and the Clean Water Act (CWA) regulate the levels of heavy metals in drinking water and surface water, respectively [76]. The EU has comprehensive directives such as the Water Framework Directive (WFD) and the Industrial Emissions Directive (IED) that limit heavy metal concentrations in water and soil. The REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) regulation also plays a crucial role in managing chemical substances, including heavy metals. Advanced wastewater treatment technologies, such as reverse osmosis and ion exchange, are widely used to remove heavy metals from industrial and municipal effluents [77]. In addition, phytoremediation and bioremediation techniques are being explored and implemented to clean up contaminated soils and water bodies. Regular monitoring programs are in place to ensure compliance with regulatory standards. On the other hand, developing countries do not have extremely strict policies over this menace. For instance, the Ministry of Environment, Forest and Climate Change (MoEFCC) has issued guidelines for the management of hazardous wastes, including heavy metals. However, enforcement remains a challenge and access to advanced treatment technologies is limited due to financial constraints. Traditional and less effective methods, such as chemical precipitation and adsorption, are more commonly used. Monitoring programs are often inadequate, and data on heavy metal concentrations in the environment are limited [78] (see **Table 3**).

Table 3. Mitigation strategies for heavy metals in developed vs. developing countries.

Aspect	Developed countries	Developing countries	References
Regulations and policies	Strict standards and comprehensive directives including EPA, and EU REACH	Guidelines and policies exist but enforcement is weak such as in India	[76]
Technological advancements	Advanced treatment technologies (reverse osmosis, ion exchange)	Limited access to advanced technologies; reliance on traditional methods	[79]
Monitoring and enforcement	Regular monitoring programs and stringent penalties	Inadequate monitoring and weak enforcement capacity	[80]
Public awareness and education	High public awareness through media and educational programs Community involvement in environmental monitoring	Lower public awareness Limited access to information and education	[81]
Healthcare infrastructure	Well-equipped healthcare facilities for early detection and treatment of metal-induced diseases Availability of specialized medical expertise	Underdeveloped healthcare infrastructure Limited access to specialized medical care	[82]
Economic impact	Higher costs for compliance with strict regulations Potential economic benefits from reduced healthcare costs and improved productivity	Lower initial costs for less stringent regulations Higher long-term costs due to health and environmental impacts	[83]
Outcomes	Significant reduction in heavy metal pollution; lower cancer rates Improved environmental quality and sustainability	Persistent contamination; higher cancer rates and health risks Higher incidence of metal-induced cancers and other health issues Deteriorating environmental quality	[84]

4. Future Perspective and Conclusion

Numerous human ailments have been linked to heavy metal contamination. These diseases arise from unintentional exposure, which can occur through internal or external causes. The emergence of various tumors is one of the main health issues linked to exposure to heavy metals. Exposure to heavy metals in the form of industrial carcinogens, cigarette smoke, and food consumption, through the diet, are the most prevalent risk factors for developing cancer. Heavy metal poisoning can cause a wide range of toxicity, from mild ailments to serious illnesses like cancer. Both have the potential to jeopardize human health in general. It is a known fact that environmental factors are most often the primary pathway leading to human exposure. Heavy metal pollution has been connected to a number of human illnesses. Unintentional exposure, which can happen for internal or external reasons, is the cause of these disorders. One of the primary health problems associated with heavy metal exposure is the development of different types of cancers. The most common risk factors for cancer include food consumption through diet, cigarette smoke, and exposure to heavy metals in the form of industrial toxins. A wide variety of toxicity, from minor symptoms to major diseases like cancer,

can be caused by heavy metal poisoning. Both can endanger people's overall health. It is well known that the main cause of human exposure is nearly always environmental causes.

Conflicts of Interest

The authors declare no conflicts of interest.

References

[1] Radfard, M., Hashemi, H., Baghapour, M.A., Samaei, M.R., Yunesian, M., Soleimani, H., *et al.* (2023) Prediction of Human Health Risk and Disability-Adjusted Life Years Induced by Heavy Metals Exposure through Drinking Water in Fars Province, Iran. *Scientific Reports*, **13**, Article No. 19080. https://doi.org/10.1038/s41598-023-46262-1

[2] Islam, M.R., Akash, S., Jony, M.H., alam, M.N., Nowrin, F.T., Rahman, M.M., *et al.* (2023) Exploring the Potential Function of Trace Elements in Human Health: A Therapeutic Perspective. *Molecular and Cellular Biochemistry*, **478**, 2141-2171. https://doi.org/10.1007/s11010-022-04638-3

[3] Chen, Y., You, L. and Sun-Waterhouse, D. (2024) Effects of Processing on the Physicochemical Characteristics and Health Benefits of Algae Products: Trade-Offs among Food Carbon Footprint, Nutrient Profiles, Health Properties, and Consumer Acceptance. *Trends in Food Science & Technology*, **147**, Article ID: 104375. https://doi.org/10.1016/j.tifs.2024.104375

[4] Abubakar, M. and Rehman, B. (2024) Roles of Mutant TP53 Gene in Cancer Development and Progression. *Proceedings of Anticancer Research*, **8**, 165-181. https://doi.org/10.26689/par.v8i5.7826

[5] Abubakar, M., Ayyoub, R., Rehman, B., Kiani, M.N., Ahmed, U., Farooq, J., *et al.* (2024) Exploring Novel Therapeutic Breakthroughs for Cancers: Potential Roles of miRNAs. *Proceedings of Anticancer Research*, **8**, 11-24. https://doi.org/10.26689/par.v8i5.6924

[6] Kong, C., Guo, Z., Song, P., Zhang, X., Yuan, Y., Teng, T., *et al.* (2022) Underlying the Mechanisms of Doxorubicin-Induced Acute Cardiotoxicity: Oxidative Stress and Cell Death. *International Journal of Biological Sciences*, **18**, 760-770. https://doi.org/10.7150/ijbs.65258

[7] Skowroń, J. (2020) Carcinogenic and Mutagenic Substances. In: Pośniak, M., Ed., *Emerging Chemical Risks in the Work Environment*, CRC Press, 127-166. https://doi.org/10.1201/9781003051152-4

[8] Khosravi-Darani, K., Rehman, Y., Katsoyiannis, I., Kokkinos, E. and Zouboulis, A. (2022) Arsenic Exposure via Contaminated Water and Food Sources. *Water*, **14**, Article 1884. https://doi.org/10.3390/w14121884

[9] Lombaert, N., Gilles, M. and Verougstraete, V. (2023) Cadmium Monitoring at the Workplace: Effectiveness of a Combination of Air- and Biomonitoring. *Toxics*, **11**, Article 354. https://doi.org/10.3390/toxics11040354

[10] Högberg, J. and Järnberg, J. (2023) Approaches for the Setting of Occupational Exposure Limits (OELs) for Carcinogens. *Critical Reviews in Toxicology*, **53**, 131-167. https://doi.org/10.1080/10408444.2023.2218887

[11] Martin, S. and Griswold, W. (2009) Human Health Effects of Heavy Metals. *Environmental Science and Technology Briefs for Citizens*, **15**, 1-6.

[12] Han, J., Ye, J., Shi, J., Fan, Y., Yuan, X., Li, R., *et al.* (2024) A Programmable Oral Nanomotor Microcapsule for the Treatment of Inflammatory Bowel Disease. *Advanced Functional Materials*, **2024**, Article ID: 2413261. https://doi.org/10.1002/adfm.202413261

[13] A. Wallace, H. and Tetyana, K. (2023) Use of Toxicology in the Regulatory Process. In: Hayes, A.W. and Kobets, T., Eds., *Hayes' Principles and Methods of Toxicology*, CRC Press, Vol1:41-Vol1:94. https://doi.org/10.1201/9781003390008-2

[14] Panaiotov, S., Tancheva, L., Kalfin, R. and Petkova-Kirova, P. (2024) Zeolite and Neurodegenerative Diseases. *Molecules*, **29**, Article 2614. https://doi.org/10.3390/molecules29112614

[15] Ozturk, M., *et al.* (2022) Arsenic and Human Health: Genotoxicity, Epigenomic Effects, and Cancer Signaling. *Biological Trace Element Research*, **200**, 988-1001.

[16] Huang, W., Zhang, Z., Qiu, Y., Gao, Y., Fan, Y., Wang, Q., *et al.* (2023) NLRP3 Inflammasome Activation in Response to Metals. *Frontiers in Immunology*, **14**, Article 1055788. https://doi.org/10.3389/fimmu.2023.1055788

[17] Priyanka, N., *et al.* (2021) Zinc Oxide Nanocatalyst Mediates Cadmium and Lead Toxicity Tolerance Mechanism by Differential Regulation of Photosynthetic Machinery and Antioxidant Enzymes Level in Cotton Seedlings. *Toxicology Reports*, **8**, 295-302. https://doi.org/10.1016/j.toxrep.2021.01.016

[18] Chowdhury, F.N. and Rahman, M.M. (2024) Source and Distribution of Heavy Metal and Their Effects on Human Health. In: Kumar, N., Ed., *Heavy Metal Toxicity*, Springer Nature Switzerland, 45-98. https://doi.org/10.1007/978-3-031-56642-4_3

[19] Zafar, A., Javed, S., Akram, N. and Naqvi, S.A.R. (2024) Health Risks of Mercury. In: Kumar, N., Ed., *Mercury Toxicity Mitigation: Sustainable Nexus Approach*, Springer, 67-92. https://doi.org/10.1007/978-3-031-48817-7_3

[20] Zhang, X., Shi, H., Tan, N., Zhu, M., Tan, W., Daramola, D., *et al.* (2023) Advances in Bioleaching of Waste Lithium Batteries under Metal Ion Stress. *Bioresources and Bioprocessing*, **10**, Article No. 19. https://doi.org/10.1186/s40643-023-00636-5

[21] Sanajou, S., Şahin, G. and Baydar, T. (2021) Aluminium in Cosmetics and Personal care Products. *Journal of Applied Toxicology*, **41**, 1704-1718. https://doi.org/10.1002/jat.4228

[22] Cohen, M.D., Bowser, D.H. and Costa, M. (2023) Carcinogenicity and Genotoxicity of Lead, Beryllium, and Other Metals. In: Chang, L.W., Ed., *Toxicology of Metals, Volume I*, CRC Press, 253-284. https://doi.org/10.1201/9781003418917-24

[23] Rehman, B., Abubakar, M., Kiani, M.N. and Ayyoub, R. (2024) Analysis of Genetic Alterations in TP53 Gene in Breast Cancer—A Secondary Publication. *Proceedings of Anticancer Research*, **8**, 25-35. https://doi.org/10.26689/par.v8i3.6720

[24] Rahimzadeh, M.R., Rahimzadeh, M.R., Kazemi, S., Amiri, R.J., Pirzadeh, M. and Moghadamnia, A.A. (2022) Aluminum Poisoning with Emphasis on Its Mechanism and Treatment of Intoxication. *Emergency Medicine International*, **2022**, Article ID: 1480553. https://doi.org/10.1155/2022/1480553

[25] Bel'skaya, L.V. and Dyachenko, E.I. (2024) Oxidative Stress in Breast Cancer: A Biochemical Map of Reactive Oxygen Species Production. *Current Issues in Molecular Biology*, **46**, 4646-4687. https://doi.org/10.3390/cimb46050282

[26] Abubakar, M. (2024) Overview of Skin Cancer and Risk Factors. *International Journal of General Practice Nursing*, **2**, 42-56. https://doi.org/10.26689/ijgpn.v2i3.8114

[27] Maltas, J., Reed, H., Porter, A. and Malliri, A. (2020) Mechanisms and Consequences of Dysregulation of the Tiam Family of Rac Activators in Disease. *Biochemical Society*

Transactions, **48**, 2703-2719. https://doi.org/10.1042/bst20200481

[28] Kumar, A., Ali, M., Kumar, R., Kumar, M., Sagar, P., Pandey, R.K., *et al.* (2021) Arsenic Exposure in Indo Gangetic Plains of Bihar Causing Increased Cancer Risk. *Scientific Reports*, **11**, Article No. 2376. https://doi.org/10.1038/s41598-021-81579-9

[29] Hussein, H.A., Thabet, A.A., Wardany, A.A. *et al.* (2024). SARS-CoV-2 Outbreak: Role of Viral Proteins and Genomic Diversity in Virus Infection and COVID-19 Progression. *Virology Journal*, **21**, 75.

[30] Huang, Z., Chen, Y. and Zhang, Y. (2020) Mitochondrial Reactive Oxygen Species Cause Major Oxidative Mitochondrial DNA Damages and Repair Pathways. *Journal of Biosciences*, **45**, Article No. 84. https://doi.org/10.1007/s12038-020-00055-0

[31] Tam, L.M., Price, N.E. and Wang, Y. (2020) Molecular Mechanisms of Arsenic-Induced Disruption of DNA Repair. *Chemical Research in Toxicology*, **33**, 709-726. https://doi.org/10.1021/acs.chemrestox.9b00464

[32] Ali, A., Riaz, S., Khalid, W., Fatima, M., Mubeen, U., Babar, Q., *et al.* (2024) Potential of Ascorbic Acid in Human Health against Different Diseases: An Updated Narrative Review. *International Journal of Food Properties*, **27**, 493-515. https://doi.org/10.1080/10942912.2024.2327335

[33] Saravanan, A., Kumar, P.S., Ramesh, B. and Srinivasan, S. (2022) Removal of Toxic Heavy Metals Using Genetically Engineered Microbes: Molecular Tools, Risk Assessment and Management Strategies. *Chemosphere*, **298**, Article ID: 134341. https://doi.org/10.1016/j.chemosphere.2022.134341

[34] Ji, H., Bi, Z., Pawar, A.S., Seno, A., Almutairy, B.S., Fu, Y., *et al.* (2024) Genomic and Epigenetic Characterization of the Arsenic-Induced Oncogenic Microrna-21. *Environmental Pollution*, **345**, Article ID: 123396. https://doi.org/10.1016/j.envpol.2024.123396

[35] Schrenk, D., Bignami, M., Bodin, L., *et al.*, (2024) Update of the Risk Assessment of Inorganic Arsenic in Food. *EFSA Journal*, **22**, e8488.

[36] Islam, R., Zhao, L., Wang, Y., Lu-Yao, G. and Liu, L. (2022) Epigenetic Dysregulations in Arsenic-Induced Carcinogenesis. *Cancers*, **14**, Article 4502. https://doi.org/10.3390/cancers14184502

[37] Ahmed, U., Abubakar, M., Ayyoub, R. and Rehman, B. (2024) Stem Cells and Exosomes-Associated Therapeutic Applications. *Journal of Clinical and Nursing Research*, **8**, 232-246. https://doi.org/10.26689/jcnr.v8i6.7012

[38] Bălă, G., Râjnoveanu, R., Tudorache, E., Motișan, R. and Oancea, C. (2021) Air Pollution Exposure—The (In)Visible Risk Factor for Respiratory Diseases. *Environmental Science and Pollution Research*, **28**, 19615-19628. https://doi.org/10.1007/s11356-021-13208-x

[39] Mohan, K.M., Chopra, A., Guddattu, V., Singh, S. and Upasana, K. (2022) Should Dentists Mandatorily Wear Ear Protection Device to Prevent Occupational Noise-Induced Hearing Loss? A Randomized Case-Control Study. *Journal of International Society of Preventive and Community Dentistry*, **12**, 513-523. https://doi.org/10.4103/jispcd.jispcd_28_22

[40] Wu, Y., Yuan, M., Wang, C., Chen, Y., Zhang, Y. and Zhang, J. (2023) T Lymphocyte Cell: A Pivotal Player in Lung Cancer. *Frontiers in Immunology*, **14**, Article 1102778. https://doi.org/10.3389/fimmu.2023.1102778

[41] Zhu, Y. and Costa, M. (2020) Metals and Molecular Carcinogenesis. *Carcinogenesis*, **41**, 1161-1172. https://doi.org/10.1093/carcin/bgaa076

[42] Alao, J.O., Fahad, A., Abdo, H.G., Ayejoto, D.A., Almohamad, H., Ahmad, M.S., *et*

al. (2023) Effects of Dumpsite Leachate Plumes on Surface and Groundwater and the Possible Public Health Risks. *Science of The Total Environment*, **897**, Article ID: 165469. https://doi.org/10.1016/j.scitotenv.2023.165469

[43] Doğanlar, O., Doğanlar, Z.B., Kurtdere, A.K., Chasan, T. and Ok, E.S. (2020) Chronic Exposure of Human Glioblastoma Tumors to Low Concentrations of a Pesticide Mixture Induced Multidrug Resistance against Chemotherapy Agents. *Ecotoxicology and Environmental Safety*, **202**, Article ID: 110940. https://doi.org/10.1016/j.ecoenv.2020.110940

[44] Zhang, H., Yan, J., Xie, Y., Chang, X., Li, J., Ren, C., *et al.* (2022) Dual Role of Cadmium in Rat Liver: Inducing Liver Injury and Inhibiting the Progression of Early Liver Cancer. *Toxicology Letters*, **355**, 62-81. https://doi.org/10.1016/j.toxlet.2021.11.004

[45] Cirovic, A. and Cirovic, A. (2022) Iron Deficiency as Promoter of Heavy Metals-Induced Acute Myeloid Leukemia. *Leukemia Research*, **112**, Article ID: 106755. https://doi.org/10.1016/j.leukres.2021.106755

[46] Lafta, M.h., Afra, A., Patra, I., Jalil, A.T., Mohammadi, M.J., Baqir Al-Dhalimy, A.M., *et al.* (2022) Toxic Effects Due to Exposure Heavy Metals and Increased Health Risk Assessment (Leukemia). *Reviews on Environmental Health*, **39**, 351-362. https://doi.org/10.1515/reveh-2022-0227

[47] Yan, L., Shi, J. and Zhu, J. (2024) Cellular and Molecular Events in Colorectal Cancer: Biological Mechanisms, Cell Death Pathways, Drug Resistance and Signalling Network Interactions. *Discover Oncology*, **15**, Article No. 294. https://doi.org/10.1007/s12672-024-01163-1

[48] Abubakar, M. (2024) Exploring the Pivotal Association of AI in Cancer Stem Cells Detection and Treatment. *Proceedings of Anticancer Research*, **8**, 52-63. https://doi.org/10.26689/par.v8i5.7082

[49] Aftab, A., Khan, Z.U. and Ali, S. (2021) Production, Kinetics and Immobilization of Microbial Invertases for Some Commercial Applications—A Review. *International Journal of Biology and Biotechnology*, **18**, 377-388.

[50] Abubakar, M., Ayyoub, R., Rehman, B., Zubair, M. and Ahmed, U. (2024) Advancing Cancer Stem Cell-Targeted Therapeutic Applications. *Proceedings of Anticancer Research*, **8**, 32-45. https://doi.org/10.26689/par.v8i5.7043

[51] Sharma, P. and Sharma, A. (2022) Heavy Metals in Ground Water Affect the Human Health Global Challenge. In: Kshatri, S.S., Thakur, K., Mamode Khan, M.H., Singh, D. and Sinha, G.R., Eds., *Computational Intelligence and Applications for Pandemics and Healthcare*, IGI Global, 139-158. https://doi.org/10.4018/978-1-7998-9831-3.ch007

[52] Balali-Mood, M., Naseri, K., Tahergorabi, Z., Khazdair, M.R. and Sadeghi, M. (2021) Toxic Mechanisms of Five Heavy Metals: Mercury, Lead, Chromium, Cadmium, and Arsenic. *Frontiers in Pharmacology*, **12**, Article 643972. https://doi.org/10.3389/fphar.2021.643972

[53] Muzaffar, S., Khan, J., Srivastava, R., Gorbatyuk, M.S. and Athar, M. (2022) Mechanistic Understanding of the Toxic Effects of Arsenic and Warfare Arsenicals on Human Health and Environment. *Cell Biology and Toxicology*, **39**, 85-110. https://doi.org/10.1007/s10565-022-09710-8

[54] Collin, M.S., Venkatraman, S.K., Vijayakumar, N., Kanimozhi, V., Arbaaz, S.M., Stacey, R.G.S., *et al.* (2022) Bioaccumulation of Lead (Pb) and Its Effects on Human: A Review. *Journal of Hazardous Materials Advances*, **7**, Article ID: 100094. https://doi.org/10.1016/j.hazadv.2022.100094

[55] Michaels, R.A. (2019) Legacy Contaminants of Emerging Concern: Lead (Pb), Flint (MI), and Human Health. *Environmental Claims Journal*, **32**, 6-45. https://doi.org/10.1080/10406026.2019.1661947

[56] Riquelme, I., Pérez-Moreno, P., Letelier, P., Brebi, P. and Roa, J.C. (2021) The Emerging Role of Piwi-Interacting RNAs (piRNAs) in Gastrointestinal Cancers: An Updated Perspective. *Cancers*, **14**, Article 202. https://doi.org/10.3390/cancers14010202

[57] Chianca, M., Panichella, G., Fabiani, I., Giannoni, A., L'Abbate, S., Aimo, A., *et al.* (2022) Bidirectional Relationship between Cancer and Heart Failure: Insights on Circulating Biomarkers. *Frontiers in Cardiovascular Medicine*, **9**, Article 936654. https://doi.org/10.3389/fcvm.2022.936654

[58] Paithankar, J.G., Saini, S., Dwivedi, S., Sharma, A. and Chowdhuri, D.K. (2021) Heavy Metal Associated Health Hazards: An Interplay of Oxidative Stress and Signal Transduction. *Chemosphere*, **262**, Article ID: 128350. https://doi.org/10.1016/j.chemosphere.2020.128350

[59] Ciosek, Ż., Kot, K., Kosik-Bogacka, D., Łanocha-Arendarczyk, N. and Rotter, I. (2021) The Effects of Calcium, Magnesium, Phosphorus, Fluoride, and Lead on Bone Tissue. *Biomolecules*, **11**, Article 506. https://doi.org/10.3390/biom11040506

[60] Yousaf, A., Tasneem, N., Mustafa, A., Fatima, R., Nabia, N., Khan, R.A., *et al.* (2021) Gastric Cancer Associated Risk Factors and Prevalence in Pakistan. *ASEAN Journal of Science and Engineering*, **1**, 73-78. https://doi.org/10.17509/ajse.v1i2.41124

[61] Mitra, S., Chakraborty, A.J., Tareq, A.M., Emran, T.B., Nainu, F., Khusro, A., *et al.* (2022) Impact of Heavy Metals on the Environment and Human Health: Novel Therapeutic Insights to Counter the Toxicity. *Journal of King Saud University—Science*, **34**, Article ID: 101865. https://doi.org/10.1016/j.jksus.2022.101865

[62] Parida, L. and Patel, T.N. (2023) Systemic Impact of Heavy Metals and Their Role in Cancer Development: A Review. *Environmental Monitoring and Assessment*, **195**, Article No. 766. https://doi.org/10.1007/s10661-023-11399-z

[63] Sadiq, I.Z. (2023) Free Radicals and Oxidative Stress: Signaling Mechanisms, Redox Basis for Human Diseases, and Cell Cycle Regulation. *Current Molecular Medicine*, **23**, 13-35. https://doi.org/10.2174/1566524022666211222161637

[64] Miziak, P., Baran, M., Błaszczak, E., Przybyszewska-Podstawka, A., Kałafut, J., Smok-Kalwat, J., *et al.* (2023) Estrogen Receptor Signaling in Breast Cancer. *Cancers*, **15**, Article 4689. https://doi.org/10.3390/cancers15194689

[65] Sonone, S.S., *et al.* (2020) Water Contamination by Heavy Metals and Their Toxic Effect on Aquaculture and Human Health through Food Chain. *Letters in Applied NanoBioScience*, **10**, 2148-2166.

[66] Riaz, M.A., Abubakar, M., Ayyoub, R., Khan, A.N. and Hameed, Y. (2024) Expression Analysis of Caspase-3 (CASP3) Gene in Leukemia Patients Using Quantitative Polymerase Chain Reaction (QPCR) and Western Blot Techniques. *Journal of Cancer Biomoleculars and Therapeutics*, **1**, 10-16. https://doi.org/10.62382/jcbt.v1i2.17

[67] Li, Z., Long, T., Wang, R., Feng, Y., Hu, H., Xu, Y., *et al.* (2021) Plasma Metals and Cancer Incidence in Patients with Type 2 Diabetes. *Science of the Total Environment*, **758**, Article ID: 143616. https://doi.org/10.1016/j.scitotenv.2020.143616

[68] Bhat, A.A., Goyal, A., Thapa, R., Almalki, W.H., Kazmi, I., Alzarea, S.I., *et al.* (2023) Uncovering the Complex Role of Interferon-Gamma in Suppressing Type 2 Immunity to Cancer. *Cytokine*, **171**, Article ID: 156376. https://doi.org/10.1016/j.cyto.2023.156376

[69] Nabavi-Rad, A., Azizi, M., Jamshidizadeh, S., Sadeghi, A., Aghdaei, H.A., Yadegar, A., *et al.* (2022) The Effects of Vitamins and Micronutrients on Helicobacter Pylori Pathogenicity, Survival, and Eradication: A Crosstalk between Micronutrients and Immune System. *Journal of Immunology Research*, **2022**, Article ID: 4713684. https://doi.org/10.1155/2022/4713684

[70] Liu, J., Huang, B., Ding, F. and Li, Y. (2023) Environment Factors, DNA Methylation, and Cancer. *Environmental Geochemistry and Health*, **45**, 7543-7568. https://doi.org/10.1007/s10653-023-01749-8

[71] Aranda-Rivera, A.K., Cruz-Gregorio, A., Arancibia-Hernández, Y.L., Hernández-Cruz, E.Y. and Pedraza-Chaverri, J. (2022) RONS and Oxidative Stress: An Overview of Basic Concepts. *Oxygen*, **2**, 437-478. https://doi.org/10.3390/oxygen2040030

[72] Indika, N.R., Senarathne, U.D., Malvaso, A., Darshana, D., Owens, S.C., Mansouri, B., *et al.* (2023) Abnormal Porphyrin Metabolism in Autism Spectrum Disorder and Therapeutic Implications. *Molecular Neurobiology*, **61**, 3851-3866. https://doi.org/10.1007/s12035-023-03722-z

[73] Olawade, D.B., Wada, O.Z., Egbewole, B.I., Fapohunda, O., Ige, A.O., Usman, S.O., *et al.* (2024) Metal and Metal Oxide Nanomaterials for Heavy Metal Remediation: Novel Approaches for Selective, Regenerative, and Scalable Water Treatment. *Frontiers in Nanotechnology*, **6**, Article 1466721. https://doi.org/10.3389/fnano.2024.1466721

[74] Lavanya, M.B., Viswanath, D.S. and Sivapullaiah, P.V. (2024) Phytoremediation: An Eco-Friendly Approach for Remediation of Heavy Metal-Contaminated Soils-A Comprehensive Review. *Environmental Nanotechnology, Monitoring & Management*, **22**, Article ID: 100975. https://doi.org/10.1016/j.enmm.2024.100975

[75] Fawole, A.A., Orikpete, O.F., Ehiobu, N.N. and Ewim, D.R.E. (2023) Climate Change Implications of Electronic Waste: Strategies for Sustainable Management. *Bulletin of the National Research Centre*, **47**, Article No. 147. https://doi.org/10.1186/s42269-023-01124-8

[76] Khanam, Z., Sultana, F.M. and Mushtaq, F. (2023) Environmental Pollution Control Measures and Strategies: An Overview of Recent Developments. In: Mushtaq, F., Farooq, M., Mukherjee, A.B. and Ghosh Nee Lala, M., Eds., *Geospatial Analytics for Environmental Pollution Modeling*, Springer Nature Switzerland, 385-414. https://doi.org/10.1007/978-3-031-45300-7_15

[77] Omoyajowo, K. (2024) Sustainable Environmental Policies: An Impact Analysis of US Regulations on Pesticides and Chemical Discharges. https://doi.org/10.2139/ssrn.4943299

[78] Singh, M., Singh, M. and Singh, S.K. (2024) Tackling Municipal Solid Waste Crisis in India: Insights into Cutting-Edge Technologies and Risk Assessment. *Science of the Total Environment*, **917**, Article ID: 170453. https://doi.org/10.1016/j.scitotenv.2024.170453

[79] Carmona, B. and Abejón, R. (2023) Innovative Membrane Technologies for the Treatment of Wastewater Polluted with Heavy Metals: Perspective of the Potential of Electrodialysis, Membrane Distillation, and Forward Osmosis from a Bibliometric Analysis. *Membranes*, **13**, Article 385. https://doi.org/10.3390/membranes13040385

[80] Axbard, S. and Deng, Z. (2024) Informed Enforcement: Lessons from Pollution Monitoring in China. *American Economic Journal: Applied Economics*, **16**, 213-252. https://doi.org/10.1257/app.20210386

[81] Mariyam, S., Satria, A.P. and Samsudin, M. (2023) Community Participation in the Prevention of Environmental Damage: Forms and Challenges. *Administrative and*

Environmental Law Review, **4**, 107-118.

[82] Halema, A.A., El-Beltagi, H.S., Al-Dossary, O., Alsubaie, B., Henawy, A.R., Rezk, A.A., *et al.* (2024) Omics Technology Draws a Comprehensive Heavy Metal Resistance Strategy in Bacteria. *World Journal of Microbiology and Biotechnology*, **40**, Article No. 193. https://doi.org/10.1007/s11274-024-04005-y

[83] Adebayo, V.I., Paul, P.O. and Eyo-Udo, N.L. (2024) Procurement in Healthcare: Ensuring Efficiency and Compliance in Medical Supplies and Equipment Management. *Magna Scientia Advanced Research and Reviews*, **11**, 60-69. https://doi.org/10.30574/msarr.2024.11.2.0106

[84] Bhat, A.A., Moglad, E., Bansal, P., Kaur, H., Deorari, M., Thapa, R., *et al.* (2024) Pollutants to Pathogens: The Role of Heavy Metals in Modulating TGF-β Signaling and Lung Cancer Risk. *Pathology—Research and Practice*, **256**, Article ID: 155260. https://doi.org/10.1016/j.prp.2024.155260